REMARKS

Claims 13, 17, and 19-42 are pending in the application. Claims 13, 17, and 19-38 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claims 39-42 are currently being examined on the merits.

Withdrawal of previous rejections

Applicants would like to thank the Examiner for withdrawing the rejection under 35 U.S.C. § 101 stated in the last Office Action. Applicants submit that, in view of the remarks made herein, the remaining rejections should also be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph:

The rejection of claims 39-42 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement was maintained. In a prior Office Action, the Examiner had asserted that "the specification does not reasonably provide enablement for immunogenic or biologically active fragments of SEQ ID NO:2, or polypeptide variants having at least 90% sequence identity to SEQ ID NO:2" (Office Action mailed February 6, 2001, page 6). In response, Applicants had amended the claims to recite specific functional limitations to the claimed variants and fragments.

The Examiner has not responded to any of these amendments or arguments in the present Office Action. Instead, the Examiner asserts that the post-filing reference, Reiter et al., submitted with the previous Response has no bearing on the instant application which allegedly did not disclose the polypeptide of SEQ ID NO:2 as a prostate stem cell antigen. The relevance of this argument is unclear, as the reference was cited in regards to the rejection under § 101, which has been withdrawn, not that under § 112. Furthermore, Reiter et al. was submitted to confirm that Applicants had correctly identified the claimed polypeptide as a stem cell antigen at the time of filing. This identification was also supported by the previously submitted BLAST results of SCAH-2 against the Genpept database which showed that all of the ten hits (seven of which are pre-filing references and three of which are post-filing references) are stem cell antigens, as well as information in the specification as filed, including the

disclosed homology to chicken stem cell antigen-2 , the presence of conserved cysteine residues, and the identification of cDNAs encoding SCAH-2 in tumor tissues. The Examiner has removed the utility rejection under 35 U.S.C. § 101 "in light of the exhibits provided by the applicant" (Office Action, p. 2). Thus there is no longer any doubt that the claimed polypeptides encode a stem cell antigen, and that this stem cell antigen is useful.

The asserted utilities for the claimed polypeptides include the use of SCAH-2 in screening, diagnosis and treatment of cancers, as asserted in the specification at, for example, p. 3, lines 9-14, and p. 18, lines 12-17 wherein the specification states that "[s]ince a high level of expression of stem cell antigens is correlated with tumors from a variety of tissues and a more malignant phenotype, the SCAH-1 and SCAH-2 proteins can be used to identify antibodies, antagonists, and inhibitors which would diminish the efficiency of local tumor growth without inducing cell proliferation." Methods for diagnostic assays and drug screening are disclosed in the specification at, for example, pp. 20-21.

Variants of SCAH-2 which retained the activity of SCAH-2 in being expressed on the surface of stem cells would clearly have the same utilities as SCAH-2 itself. An immunogenic fragment of SEQ ID NO:2 is obviously useful for producing the antibodies described above. These antibodies are useful in the diagnostic assays described at p. 20, lines 5-29. Biologically and immunologically active fragments are also useful in drug screening techniques ("SCAH, its catalytic or antigenic fragments or oligopeptides, can be used for screening therapeutic compounds in any of a variety of drug screening techniques" p. 20, lines 33-34). Thus there can be no doubt that the claimed variants and fragments all have utility, and that one of ordinary skill in the art would know how to use these variants and fragments without any undue experimentation.

In a prior Office Action, the Examiner asserted that "Given the lack of guidance in the specification for choosing which amino acid residues of SEQ ID NO:2 will tolerate substitution, either separately or in groups, and which specific amino acids can be substituted in at any specified location, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the claimed invention" (Office Action mailed February 6, 2001, pages 7-8). In support of this assertion, the Examiner cited references that gave examples where single amino acid changes altered the function of a protein. These references are not relevant to the instant case,

because the claims specify "an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:2, wherein said amino acid sequence is expressed on the surface of stem cells." Only variants which retain this activity are claimed, not all possible variants. One of skill in the art need only test whether a naturally occuring variant, which can be identified through methods well known in the art and described in the specification (at, for example, p. 22, lines 1-7) has the required activity. Assays for determining the presence and distribution of SCAH-2 molecules in cell populations are described in the specification at, for example, p. 38, lines 10-12. The specification has also disclosed residues which are conserved across a number of stem cell antigens and thus likely to be important for function, for example, the conserved cysteine residues (see the specification at p. 6, lines 15-19). Thus the skilled artisan would have additional guidance in making and using the claimed variants.

With respect to the claimed biologically active fragments, the Examiner has asserted that "one of skill in the art could not anticipate what amino acid sequence(s) would retain the function of the SCAH-2 polypeptide" and cited references pertaining to the three-dimensional structures of proteins (Office Action mailed February 6, 2001, page 8). Once again, these references are not relevant as the claims recite "a biologically-active fragment of the amino acid sequence of SEQ ID NO:2, wherein said biologically-active fragment is expressed on the surface of stem cells," an activity for which the specification has provided assays. It is not necessary for the specification to list the sequences of all the biological fragments encompassed by the claims, since one of ordinary skill in the art would be able to identify and use those biologically active fragments retaining the required activity by following the guidance in the specification, without any undue experimentation.

With respect to the claimed immunologically active fragments, the Examiner has asserted that the specification does not teach any examples of immunologically active fragments. The Examiner further asserted that "[t]he determination of an immunogenic fragment is clearly a non-trivial enterprise, and without further guidance from the specification on known sequences of the SEQ ID NO:2 polypeptide which have been determined to be immunogenic fragments in a specific organism, it would require undue experimentation for one of skill in the art to make and use the invention as claimed" (Office Action mailed February 6, 2001, p.10).

Applicants respectfully point out that the generation of antibodies to proteins is well known in the art and is routinely successful without knowledge of the crystal structure of the protein, in contrast to the assertions of the Examiner. In addition, the specification provides further guidance as to the selection of immunogenic fragments. See, for example, p. 38, lines 15-21, wherein the specification describes software programs used to determine regions of high immunogenicity and also discloses that appropriate epitopes may include "those near the C-terminus or in hydrophilic regions." A hydrophobicity plot for SCAH-2 is provided in Figure 5. Applicants note that Paul et al., a reference cited by the Examiner, concurs that "hydrophilicity has been proposed as a second indication of immunogenicity" and that of 12 proteins tested, "the most hydrophilic site of each protein was indeed one of the antigenic sites" (Paul et al., p. 249). Thus even the evidence cited by the Examiner confirms that based upon the guidance provided in the specification, one of ordinary skill in the art would be able to make and use immunogenic fragments of SEQ ID NO:2 without any undue experimentation.

Rejections under 35 U.S.C. § 102:

The rejection of claim 39 under 35 U.S.C. § 102 was maintained. The Examiner asserts that claim 39 is anticipated by any of Wilkie et al (Genomics, 1993), Wray et al. (Gene, 1993), Burton (Nature, 1993), Gama et al. (Mol. Microbiol., 1992), Birkeland (Can. J. Microbiol., 1994), or Arendt et al. (Appl. Environ. Microbiol., 1994). Claim 39 recites "an immunogenic fragment comprising at least 5 contiguous amino acids of SEQ ID NO:2." The Examiner asserts that "all of the cited references provide polypeptides comprising at least 5 contiguous amino acids of SEQ ID NO:2" (Final Office Action, p. 3).

This is simply incorrect. Applicants have previously submitted sequence alignments using the CLUSTALW algorithm between SEQ ID NO:2 and the polypeptides of Wray et al. and Burton. These are once again submitted together with alignments of SEQ ID NO:2 with the polypeptides of Wilkie et al. and Birkeland (See Exhibit A). It was not possible to perform alignments for the other two references because it could not be determined which of over 40 possible proteins was referred to in the case of Gama et al., and because no protein sequences were found in the GenBank database associated with Arendt et al.

It can be plainly seen from these alignments that there is no region of greater than 4 contiguous amino acids that is shared by SEQ ID NO:2 and any of the reference polypeptides. Applicants note that these regions are too short for use as immunogenic peptides. The experiments described in Paul et al., for example, used peptides from 6 to 14 residues long (Paul et al., p. 250). Applicants further note that the Examiner has not submitted any sequence alignments to provide evidence for her claim that the references all provide polypeptides comprising at least 5 contiguous amino acids of SEQ ID NO:2. In the absence of any such evidence, and the presence of clear and convincing evidence from Applicants that the reference polypeptides do not comprise the claimed fragments, the Examiner must conclude that these reference polypeptides do not anticipate the claims. Withdrawal of the rejection of claim 39 under 35 U.S.C. § 102 is therefore respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650)855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE GENOMICS, INC.

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Diana Hamlet-Cox
Reg. No. 33,302
Direct Dial Telephone: (650) 845-4639

3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886